

Case Report

Rheumatological picture of a patient having multifocal osteonecrosis associated with sickle cell anemia: a case study

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Abstract: Avascular necrosis (AVN) is a critical health condition associated with local death of the bone tissue resulting in multifocal osteonecrosis (MFON). After a prior patient's consent, we present a case of sickle cell anemia associated with severe MFON that affected both long bones and short bones. She had a positive history of DVT. Initially, she presented with generalized severe bone pain with fever for seven days that got worse on the day of admission, a picture suggestive of sickle cell anemia-induced vaso-occlusive crisis. She was treated with adequate hydration, morphine, enoxaparin (a low molecular weight heparin), paracetamol and ceftriaxone. She got improved on treatment. On 5th day after admission, she developed sudden severe local tenderness at the distal tibia above the medial malleoli in both legs and she was unable to put a weight on her feet and could not stand up or walk. Plain X-ray films were not diagnostic. Complete liver function tests and kidney function tests were normal. The patient had leukocytosis, high serum urate and high serum LDH (may reflect cellular damage in bone cells). MRI scans revealed an evidence of bilateral multiple avascular necrosis in both femoral heads, left shoulder, left knee, and pelvic bones were evident. The patient's condition was evaluated and the diagnosis of MFON associated with sickle cell crisis was established. This patient responded well to same treatments and her condition got improved. In conclusion, MFON should be considered after vaso-occlusive crisis of sickle cell anemia. Plain X-ray is non-conclusive in diagnosing bony lesions induced by AVN while MRI is diagnostic.

Keywords: MFON, sickle cell anemia, leukocytosis, LDH, feet AVN, enoxaparin, uric acid, LDH

Introduction

Avascular necrosis is a critical health condition associated with local death of the bone tissue resulting in multifocal osteonecrosis (MFON) [1, 2]. MFON occurs more among some ethnic populations e.g. African Americans. The incidence is quite lower among Hispanic, non-Hispanic white and Asian/Pacific Islanders [3]. Osteonecrosis is a disabling disorder that frequently occurs in the younger population aged from 20 to 50 years [4]. MFON may occur in distinct anatomical sites e.g. the shoulder, knee, hip, ankle or where osteonecrosis results in disabling all these anatomical sites [5]. The use of corticosteroids has been reported as a major

risk factor of MFON. Other risk factors include infection with human immunodeficiency virus, systemic lupus erythematosus, coagulation abnormalities, renal failure, multiple sclerosis, inflammatory bowel diseases, Sjogren's syndrome, leukemia, lymphoma, and sickle cell disease [1, 2, 6].

Sickle cell disease is more common among African American children than among Hispanic American children. Sickle cell crisis is the acute painful crisis that consists of many phases: Phase I lasts about three days and is associated with a low-intensity aching pain. The patient may also report numbness and paresthesia. The aching increases rapidly in Phase II, which

is due to local tissue infarct from vaso-occlusion. Phase III goes along with constant severe pain that may be associated with a fever due to post-infarct inflammatory responses. Phase III usually lasts three to five days. This is followed by the resolution of the vaso-occlusive crisis in phase IV over one to two days. Unfortunately, vaso-occlusive crisis may create a vicious cycle. Vaso-occlusive crisis often requires hospitalization due to several acute associated conditions e.g. aplastic crisis, splenic sequestration crisis, hyperhemolytic crisis, hepatic crisis, dactylitis, and acute chest syndrome. Other acute complications of sickle cell disease include avascular necrosis, osteomyelitis, stroke, pneumonia, meningitis, sepsis, priapism, and venous thromboembolism [7-9].

MFON diagnosis is challenging since most patients do not display the classic symptoms, making it difficult to identify the disease's incidence for patients with other underlying diseases. Unfortunately, plain X-ray films are not so sensitive to diagnosing asymptomatic MFON. The gold standard procedure for diagnosing MFON is Magnetic Resonance Imaging (MRI) because of its sensitivity, accuracy, and specificity [10]. MRI limitations include high costs, time consumption and the need for optimizing the procedure in screening symptomatic and asymptomatic patients. Short-time inversion recovery (STIR) is a diagnostic procedure recommended to supplement MRI [11]. However, for sensitivity and accuracy, more research is required to develop more informed screening procedures.

MFON has no typical symptoms. However, MFON presentation may depend on the affected joints sites e.g. the hip, knee, elbow and ankle in addition to affected bones as the calcaneus, and the tarsal navicular bones [12]. The most symptomatic sites are the knee, ankle, and hip. The symptoms are characterized by pain and lesions where the total number of lesions is higher in the hip, followed by the knee and shoulder at least among these three anatomical sites [1, 2, 6, 10, 11]. These osteonecrotic lesions appear consecutively among patients with high doses of corticosteroids. Based on other risk factors e.g. sickle cell disease and systemic lupus erythematosus, the total number of lesions follows the same sequence. The lesions are observed following a radiographic evaluation, showing the joints

affected by the disease. Seijas et al. note that femoral head's necrosis is more prevalent among older persons [13]. Lamb et al. noted that the impact of MFON might be due to the weight impacted on the hip bone, increasing the risk of lesions or an injury [14].

This case study aims to shed light on the relevant predisposing factors, suitable diagnostic imaging tools and effective therapies of AVN.

Case presentation

A 26-years old Saudi female presented to the emergency department at King Fahd Hospital (Al-Madinah, Saudi Arabia) with the main complaint of generalized severe bone pain with fever for seven days that got worse on the day of admission. The patient had a history of left leg deep vein thrombosis (DVT) that required blood exchange transfusion eight months ago. She also had a history of left knee septic arthritis that required surgical debridement four months ago. She was well-known to have sickle cell anemia since childhood. She was also previously diagnosed with vaso-occlusive crisis (a complication of sickle cell anemia) precipitated by upper respiratory tract infection. She had no history of fever or any changes of her skin color. There was no history of chest, cardiovascular or abdominal symptoms. However, she had multiple previous hospital admissions with the diagnosis of vaso-occlusive crisis (a complication of sickle cell anemia) over the last several years. Her positive data are listed in **Table 1**.

Upon admission, physical examination revealed that the patient had an average body built, presenting with severe feet pain and the vital signs were stable (Temperature 36.5°C, Blood pressure 107/61 mmHg, heart rate 120 beats/min) and oxygen saturation 99% on room air. Chest examination was clinically free and chest X-ray was normal (**Figure 1**). Lower limb examination revealed apparently normal legs, no local swelling, and no signs of DVT. The patient was thoroughly investigated. Complete liver function tests (serum ALT, AST, albumin, globulin, total protein and bilirubin) and kidney function tests (serum urea, creatinine and uric acid) were done. Complete blood count and coagulation screen (bleeding time and activated partial thromboplastin time) were done. She had leukocytosis, anemia, high serum LDH and uric acid, normal coagulation screen and normal platelets count.

Rheumatological MFON associated with sickle cell anemia

Table 1. Positive data in this patient

- Positive history of sickle cell anemia
- Positive history of vaso-occlusive crisis
- Positive history of bilateral multiple sites of avascular necrosis in both femoral heads, left shoulder, left knee, and pelvic bones
- Positive history of deep vein thrombosis (DVT)
- Leucocytosis
- Severe feet pain, unable to put weight on her feet and could not stand up and walk
- Severe local tenderness at the distal tibia about four centimeters above the medial malleoli in both legs



Figure 1. Chest X-ray of the patient showing normal findings.

The diagnosis was vaso-occlusive crisis due to sickle cell anemia. Vaso-occlusive attacks were very painful for which she was treated with adequate hydration therapy, morphine (10 mg intramuscularly every 4 hours and enoxaparin (a low molecular weight heparin) 40 mg subcutaneously once a day, paracetamol 1 g intravenously (when needed) and ceftriaxone 2 g intravenously once daily for 5 days). The patient improved and most of her symptoms subsided after four days.

On 5th day after admission, the patient suddenly developed acute severe bilateral feet pain preventing her from walking, standing or putting a weight on her feet. The feet pain was too severe and was causing her to cry. The feet pain continued to be dull in nature and aggravated by standing or putting a weight on her



Figure 2. X-ray of both feet and legs of the patient showing normal findings. X-ray was not conclusive during the severe pain attacks of vaso-occlusive crisis of sickle cell anemia.

feet over the last two years. The patient had a history of bilateral multiple avascular necrosis (AVN) in both femoral heads, left shoulder, left knee, and pelvic bones.

Serum LDH was estimated. Plain X-ray and MRI scans were done to scan multiple bones in the upper limbs, lower limbs and pelvis. Complete blood count and coagulation screen (bleeding time and activated partial thromboplastin time) were done.

There was severe local tenderness at the distal tibia about four centimeters above the medial malleoli in both legs. Arterial pulsation was normal in both legs and feet. Also, Ankle and feet examinations revealed no joint deformity or swelling, normal range of motion in both ankles,

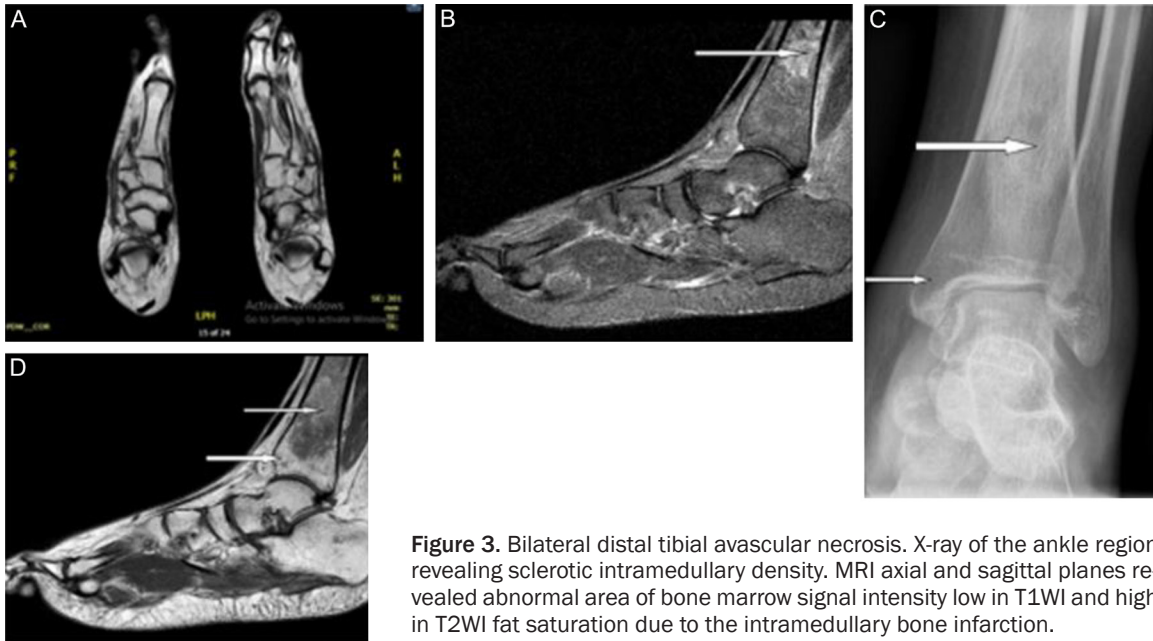


Figure 3. Bilateral distal tibial avascular necrosis. X-ray of the ankle region revealing sclerotic intramedullary density. MRI axial and sagittal planes revealed abnormal area of bone marrow signal intensity low in T1WI and high in T2WI fat saturation due to the intramedullary bone infarction.

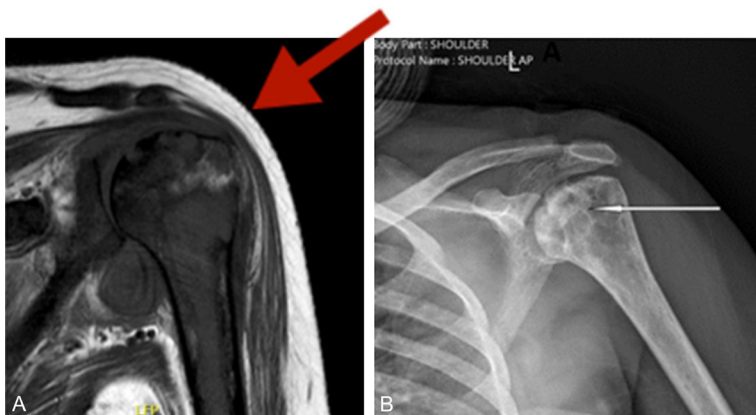


Figure 4. Manifestations of AVN of the humeral head. Left shoulder X-ray revealed heterogeneous sclerosis of the left humeral head due to avascular necrosis. Left shoulder coronal MRI revealing evidence of bone marrow edema and “double line sign” denoting avascular necrosis of the head of the humerus (denoting recent infarction new crisis on top of the old ones). (So, recent crisis of the bone infarction and avascular necrosis are diagnosed by MRI while plain X ray can detect the sclerosis related to the sequelae of the old ones).

no signs of arthritis (swelling, hotness, and tenderness), and severe local tenderness at both heels upon applying mild pressure. The patient was unable to put weight on her feet and could not stand up and walk because of severe pain in her feet (**Figure 2**). Subsequently, MRI was done and revealed multiple AVN in both feet (**Figure 3**), humeral heads (**Figure 4**), bone infarct in humeral medullary (**Figure 5**), tibial intramedullary infarction (**Figure 6**), bilateral

pelvic bone AVN (**Figure 7**) and bilateral femoral heads AVN (**Figure 8**). The patient had leukocytosis (28,900 cells/mm³) and a high serum uric acid and LDH (**Table 2**).

Then, a rheumatology consultation was done for her new symptoms. The patient’s condition was evaluated and the diagnosis of AVN associated with vaso-occlusive sickle cell crisis was confirmed. The case improved after receiving anti-coagulants (enoxaparin), antibiotics, arterial dilators, hypolipidemic drugs and physiotherapy. The patient gave her consent on publishing her clinical data.

Discussion

Risk factors for MFON include a high dose of corticosteroids intake, inflammatory conditions (as COVID-19), chronic alcohol use and sickle cell disease [5, 10, 11, 15, 16]. The high incidence is linked to using corticosteroids in managing the diseases, which a major risk factor [4]. In a study conducted among 176 patients diagnosed with SARS, approximately 21% of

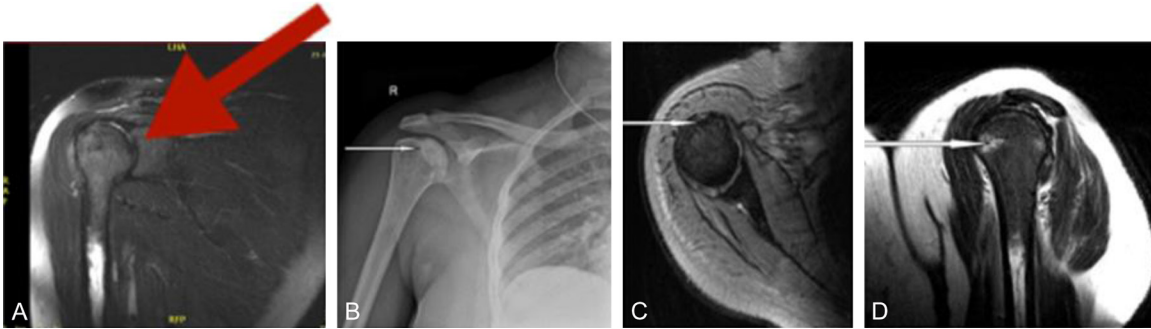


Figure 5. Right humeral medullary infarction and avascular necrosis. A, C and D. Coronal, axial and sagittal MRI views of the shoulder revealing “Double line sign” in the humerus head with a rim of edema denoting a recent attack of avascular necrosis and intramedullary areas of high T2WI area of bone marrow edema (denoting recent bone infarction). B. X ray shoulder revealed humerus having heterogeneous areas of sclerosis denoting old avascular necrosis.



Figure 6. A. Plain X-ray showing left upper tibial intramedullary, distal femoral intramedullary and medial condylar areas of heterogeneous sclerosis due to the old bone infarction. B-E. Axial and coronal MRI sequences revealing areas of bone marrow edema at the distal femur intramedullary region and the medial condyle related to the new crisis of bone infarction.

the investigated patients had MOFN [4]. In another study conducted among 200 patients with sickle cell disease, 44% of participants had MOFN.

Some patients may develop AVN while on anti-coagulation therapy. Furthermore, sickle cell anemia is a well-known cause of AVN.

Herein, we present a case of AVN that affected both long bones and short bones. Plain X-ray was non-conclusive in diagnosing bony lesions induced by AVN. This case was associated with vaso-occlusive crisis of sickle cell anemia. Our case is one of the most severe cases of MFON. She presented with bilateral multiple avascular necrosis in both femoral heads, left shoul-

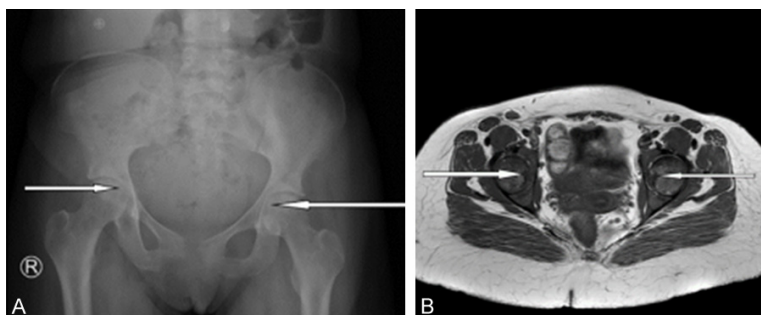


Figure 7. Bilateral pelvic bone avascular necrosis. X-ray of both hip regions revealed linear sclerosis of avascular necrosis affecting both femoral heads. MRI of both femur heads showed linear high signal intensity of edema due to avascular necrosis.

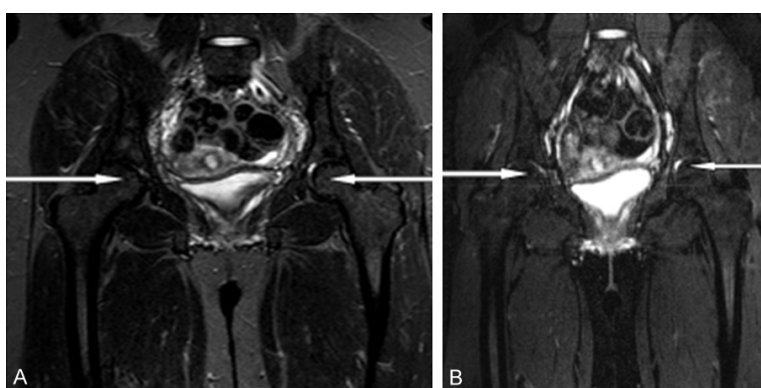


Figure 8. Bilateral T2WI sequences with and without fat saturation. Coronal view showed femoral head linear high signal intensity denoting stage II avascular necrosis.

Table 2. Complete blood count and laboratory results on the day of admission

Tests	Results	Reference Range
White blood cell (WBC)	28.9	(4-10)×10 ⁹ /L
Red blood cell (RBCs)	2.56	(3.8-4.8)×10 ¹² /L
Hemoglobin	9.6	(12-15) g/dL
Hematocrit (HTC)	28.5	(36-46)%
Mean corpuscular volume (MCV)	87.4	(83-101) fL
Mean corpuscular hemoglobin (MCH)	29.4	(27-32) pg
Platelets	410	(150-410)×10 ⁹ /L
Aspartate Aminotransferase (AST)	27	(10-50) U/L
Alanine Aminotransferase (ALT)	14	(0-41) U/L
Lactic Acid Dehydrogenase (LDH)	273	(100-190) U/L
Creatinine	53.12	(44-115) mmol/L
Urea	3.8	(2.5-8.3) mmol/L
Uric Acid	482	(155-357) umol/L

der, left knee, and pelvic bones. There was positive history of DVT, severe feet pain and she was unable to put weight on her feet and

could not stand up and walk. There was severe local tenderness at the distal tibia about four centimeters above the medial malleoli in both legs.

This case study clearly confirmed the vital role of MRI in diagnosing bone AVN where plain X-ray films did not give significant findings. There have been controversies in defining management strategies for treating MOFN due to the challenges in establishing the prognosis of the lesions and the variable progress of osteonecrosis in different joints. That may hinder determining the order of treatments. Petek et al. recommend early screening to prevent femoral head necrosis progress [17]. According to Sun et al., joint-preservation and conservative treatment options at early stages can help in managing avascular necrosis [18].

Leukocytosis in this patient may reflect a severe secondary infection or a related inflammatory process that improved after antibiotics intake. High serum urate may reflect increased death of bone cells (AVN) causing release of nucleic acids from dying cells that is further metabolized into urate. High serum LDH may reflect cellular damage in bone cells caused by osteonecrosis. Fortunately, this patient responded well to enoxaparin in agreement with a previous report [16]. According to Beckmann et al., enoxaparin is effective in managing corticosteroid-related avascular necrosis [16].

For the authors, this case study is a straight forward association between AVN and sickle cell anemia complications. Proper management of

sickle anemia-induced crises is quite vital in treating AVN. Our case study also highlighted the vital role of MRI in diagnosing and evaluating AVN extent and tissue damage. We do appreciate the therapeutic roles of low molecular weight heparins (enoxaparin) in the management of AVN.

In conclusion, MFON should be considered after vaso-occlusive crisis of sickle cell anemia. Plain X-ray was non-conclusive in diagnosing bony lesions induced by AVN while MRI is diagnostic.

Disclosure of conflict of interest

None.

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